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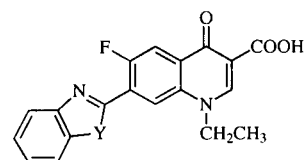
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The fluoroquinolones, 7-benzoxazol-2-yl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 7-benzothiazol-2-yl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, were synthesized. The compounds were obtained by use of the Gould-Jacobs route to the quinoline ring system. The required anilines, 3-benzoxazol-2-yl-4-fluorophenylamine and 3-benzothiazol-2-yl-4-fluorophenylamine were obtained by the cyclodehydration reaction of 5-amino-2-fluorobenzoic acid with 2-aminophenol or 2-aminothiophenol respectively using polyphosphoric acid.

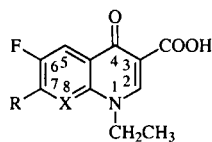
J. Heterocyclic Chem., **35**, 1301 (1998).

Introduction.

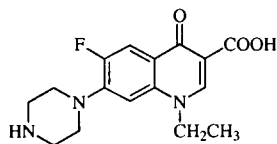
Of the possible positions for modification of the fluoroquinolone general structure **1**, substitutions at position C-7 have been very rewarding. Modifications at this position have led to numerous investigational and clinically significant compounds, such as norfloxacin **2** [1], irloxacin **3** [2], pefloxacin **4** [3].



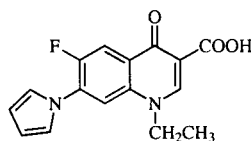
5
a, Y = O
b, Y = S



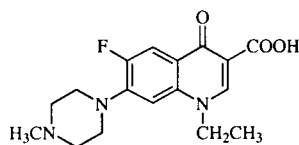
1, N-1-ethylfluoroquinolone
basic structure
X = N or CH



2, Norfloxacin



3, Irloxacin



4, Pefloxacin

The C-7 group must be a cyclic basic nitrogen containing group for best activity [4,5]. Five and six member heterocyclic systems (aliphatic or aromatic) at C-7, with or without small appended substituents, generally have yielded highly active compounds [4,5]. However, there is some limited flexibility in the size of the C-7 substituent and some bulkier groups have yielded very active compounds [6]. The substituent at position C-7 has been shown to determine to a great extent the potency, antibacterial spectrum, solubility and pharmacokinetics of the molecule [6,7].

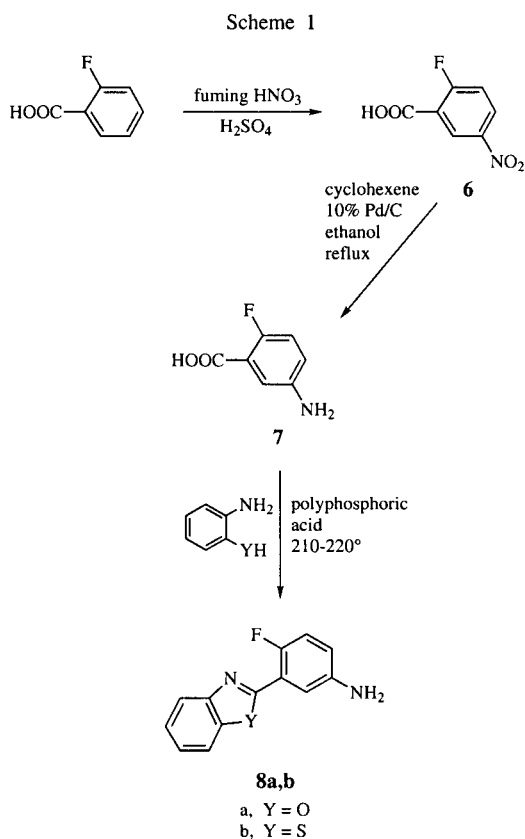
We became interested in the synthesis of fluoroquinolones which have C-7 benzoxazol-2-yl and benzothiazol-2-yl groups as represented in **5** in order to know the influence of these groups on the antibacterial activity.

These fluoroquinolones are similar to irloxacin except that a C-7 heteroaromatic group is attached through a carbon to carbon bond. A relatively small number of fluoroquinolones with C-7 heteroaromatic substituents connected through a carbon to carbon bond have been investigated, some of which are highly active compounds [6-11].

Chemistry.

The synthesis of the target compounds was pursued by use of the Gould-Jacobs route to the quinoline ring system [12]. The required aromatic amines for the Gould-Jacobs synthesis were synthesized as outlined in Scheme 1. Nitration of 2-fluorobenzoic acid with fuming nitric acid gave 2-fluoro-5-nitrobenzoic acid **6**. Upon mixing with an authentic sample of 2-fluoro-5-nitrobenzoic acid, the purified nitration product **6** showed no depression of the melting point. The nitration product **6** was converted to 5-amino-2-fluorobenzoic acid **7** by treatment with cyclohexene/10% palladium on carbon in ethanol [13]. Reaction of **7** with 2-aminophenol and 2-aminothiophenol in the presence of polyphosphoric acid [14] gave 3-benzoxazol-2-yl-4-fluorophenylamine **8a** and 3-benzothiazol-2-yl-4-fluorophenylamine **8b** respectively.

Scheme 2 shows the synthesis of the target fluoroquinolones by the Gould-Jacobs route. The amines **8a** and **8b** were condensed with diethyl ethoxymethylenemalonate to yield the anilinomethylenemalonates **9a** and **9b**. The anilinomethylenemalonates **9a** and **9b** were cyclized in refluxing diphenyl ether to give the 4-hydroxyquinoline-3-carboxylates **10a** and **10b**. Compounds **10a**



and **10b** were alkylated by treatment with ethyl iodide in the presence of potassium carbonate in *N,N*-dimethylformamide to yield the fluoroquinolone esters **11a** and **11b**. Subsequently, the fluoroquinolone esters **11a** and

11b were hydrolyzed, using aqueous sodium hydroxide, to the fluoroquinolones **5a** and **5b**.

Cyclization of **9a** and **9b** to **10a** and **10b** was indicated by ^1H nmr. The ^1H nmr spectra of both **10a** and **10b** show a doublet for the C-5 hydrogen (8.65 δ , $J = 10$ Hz for **10a** and 8.69 δ , $J = 11$ Hz for **10b**). Both **10a** and **10b** show a doublet in the ^1H nmr spectrum for the C-8 hydrogen (9.45 δ , $J = 6$ Hz and 9.31 δ , $J = 5$ Hz respectively). Alkylation on the nitrogen of **10a** and **10b** was shown by the ir spectra of **11a** and **11b**. Both **11a** and **11b** show two carbonyl peaks (1680 cm^{-1} and 1651 cm^{-1} for **11a** and 1685 cm^{-1} and 1638 cm^{-1} for **11b**).

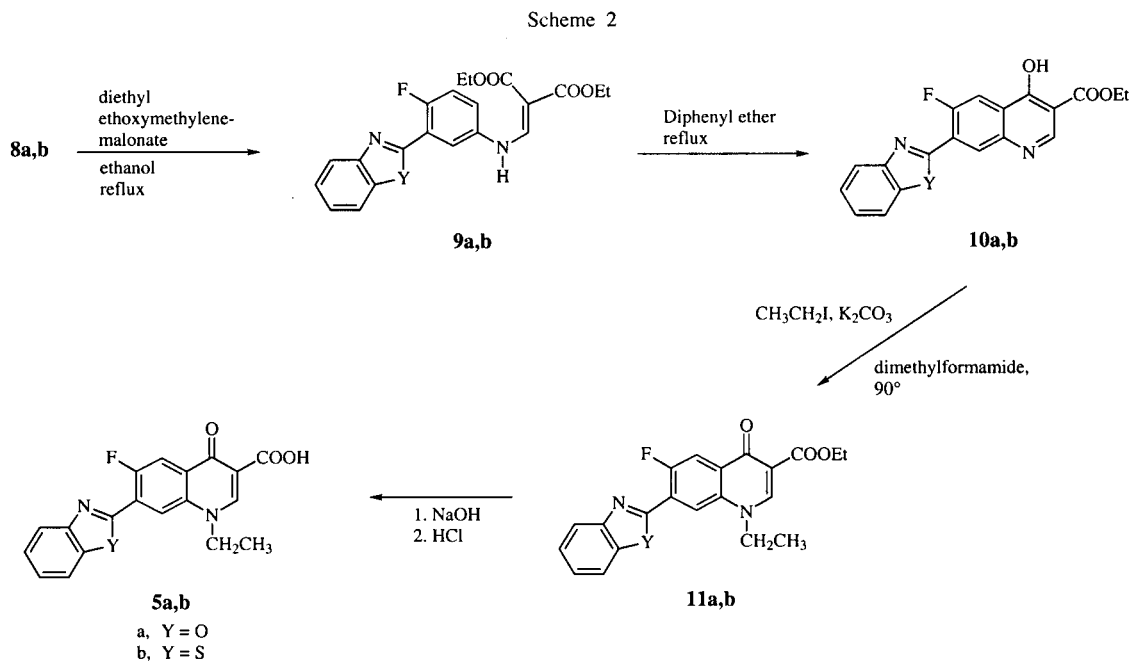
The antibacterial analysis of the fluoroquinolones **5a** and **5b** is forthcoming and will be reported elsewhere.

EXPERIMENTAL

Melting points were determined in open capillary tubes using an electrothermal melting point apparatus and are uncorrected. The proton nmr spectra were determined on a Varian EM360L 60 MHz spectrometer or a Nicolet NT360 360 MHz spectrometer. Chemical shifts are expressed in ppm (δ) relative to tetramethylsilane. The infrared spectra were determined as potassium bromide disk with a Perkin-Elmer 1605 FTIR spectrometer. Elemental analysis was performed by Galbraith Laboratories, Knoxville, TN and are within 0.4%. Thin layer chromatography (tlc), using silica gel plates, was used to ascertain purity of compounds.

2-Fluoro-5-nitrobenzoic Acid (**6**).

To a solution of 2-fluorobenzoic acid (70.0 g, 500 mmoles) and concentrated sulfuric acid (272 ml), was added a mixture of



fuming nitric acid (38.4 ml, 80.0 moles) and concentrated sulfuric acid (114 ml). After addition of the acid mixture, the reaction mixture was heated at 80-90° for 45 minutes, cooled, poured into ice, filtered, washed with water and dried to yield compound **6** (81 g, 88%) [15]. The compound was recrystallized from ethanol, mp 141-142°; ir (potassium bromide): 3408-2111, 1695, 1631, 1531, 1488, 1455, 1423, 1292, 1147, 1076, 948, 921, 850, 743, 699, 672, 634 cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.35-9.00 (m, 3H, aromatic), 11.68 (s, 1H, COOH).

Anal. Calcd. for C₇H₄FNO₄: C, 45.42; H, 2.18; N, 7.57. Found: C, 45.13; H, 2.09; N, 7.48.

A mixture of this sample with an authentic sample purchased from Aldrich Chemical Company showed no depression of the melting point, mp 141-142°.

5-Amino-2-fluorobenzoic Acid (7).

A mixture of 10% palladium on carbon (27 g), ethanol (100 ml), compound **6** (37.0 g, 200 mmoles) and cyclohexene (450 ml) was refluxed for six hours. The mixture was filtered to remove the catalyst. The liquid was removed at the rotary evaporator under reduced pressure to leave the product, compound **7** (28 g, 89%). The compound was recrystallized from methanol, mp 190-192°, lit 190 [16]; ir (potassium bromide): 3417-2182, 1650, 1636, 1437, 1374, 1200, 830, 800, 767, 673, 482 cm⁻¹; ¹H nmr (dimethyl sulfoxide-d₆): δ 3.18 (s, 3H, NH₃⁺), 6.72-7.06 (m, 3H, aromatic H).

Anal. Calcd. for C₇H₆FNO₂: C, 54.20; H, 3.90; N, 9.03. Found: C, 54.45; H, 4.11; N, 9.92.

3-Benzoxazol-2-yl-4-fluorophenylamine (8a).

Equimolar amounts of 2-aminophenol (5.50 g, 50.0 mmoles) and compound **7** (7.75 g, 50.0 mmoles) were added to 36 g of polyphosphoric acid. The mixture was heated to 220° and maintained at this temperature for 4 hours. The mixture was cooled, poured into water and neutralized with 3M sodium hydroxide. The solid was collected by filtration and treated with 5% hydrochloric acid followed by filtration. The filtrate was neutralized with 3M sodium hydroxide. The solid was collected, washed with water, and dried to obtain **8a** (10.0 g, 88%). The compound was recrystallized from ethanol, mp 158-160°; ir (potassium bromide): 3468, 3329, 1629, 1544, 1489, 1451, 1249, 1218, 819, 748 cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.74 (s, 2H, NH₂), 6.78-7.82 (m, 7H, aromatic H).

Anal. Calcd. for C₁₃H₉FN₂O: C, 68.42; H, 3.98; N, 12.27. Found: C, 68.20; H, 3.99; N, 12.21.

3-Benzothiazol-2-yl-4-fluorophenylamine (8b).

Equimolar amounts of 2-aminothiophenol (6.25 g, 50.0 mmoles) and compound **7** (7.75 g, 50.0 mmoles) were added to 36 g of polyphosphoric acid. The mixture was heated to 210° and maintained at this temperature for 4 hours. The mixture was cooled, poured into water and neutralized with 3M sodium hydroxide. The solid was collected by filtration and treated with 5% hydrochloric acid followed by filtration. The filtrate was neutralized with 3M sodium hydroxide. The solid was collected by filtration, washed with water, and dried to obtain **8b** (10.6 g, 87%). The compound was recrystallized from ethanol, mp 136-138°; ir (potassium bromide): 3375, 3301, 1511, 1466, 1317, 1208, 810, 751, 723, 692 cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.72 (s, 2H, NH₂), 6.76-8.14 (m, 7H, aromatic H).

Anal. Calcd. for C₁₃H₉FN₂S: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.67; H, 3.83; N, 11.26.

Diethyl 2-(((3-Benzoxazol-2-yl-4-fluorophenyl)amino)methylene)propane-1,3-dioate (**9a**).

Equimolar amounts of compound **8a** (5.70 g, 25.0 mmoles) and diethyl ethoxymethylenemalonate (6.50 g, 25.0 mmoles) were heated in ethanol (25 ml) at reflux for 2 hours. The ethanol was removed at the rotary evaporator under reduced pressure. The product was recrystallized from ethyl acetate to yield compound **9a**, (8.60 g, 86%), mp 177-178°; ir (potassium bromide): 3249, 1708, 1654, 1613, 1598, 1510, 1305, 1243, 1223, 1079, 803, 749, 519 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.35 (t, J = 7, 3H, CH₃CH₂), 1.40 (t, J = 7, 3H, CH₃CH₂), 4.28 (q, J = 7, 2H, CH₂CH₃), 4.33 (q, J = 7, 2H, CH₂CH₃), 7.24-8.04 (m, 6H, aromatic H), 8.52 (d, J = 14, 1H, -NH-CH=C), 11.16 (d, J = 14, 1H, -NH-CH=C).

Anal. Calcd. for C₂₁H₁₉FN₂O₅: C, 63.31; H, 4.81; N, 7.03. Found: C, 63.10; H, 4.90; N, 6.93.

Diethyl 2-(((3-Benzothiazol-2-yl-4-fluorophenyl)amino)methylene)propane-1,3-dioate (**9b**).

Equimolar amounts of compound **8b** (6.10 g, 25.0 mmoles) and diethyl ethoxymethylenemalonate (5.40 g, 25.0 mmoles) were heated in ethanol (25 ml) at reflux for 2 hours. The ethanol was removed at the rotary evaporator under reduced pressure. The product was recrystallized from ethyl acetate to yield compound **9b** (7.56 g, 73%), mp 162-164°; ir (potassium bromide): 3238, 1709, 1650, 1625, 1601, 1512, 1435, 1309, 1248, 1207, 1070, 804, 757, 731, 524 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.36 (t, J = 7, 3H, CH₃CH₂), 1.40 (t, J = 7, 3H, CH₃CH₂), 4.28 (q, J = 7, 2H, CH₂CH₃), 4.35 (q, J = 7, 2H, CH₂CH₃), 7.20-8.28 (m, 7H, aromatic H), 8.55 (d, J = 14, 1H, -NH-CH=C), 11.16 (d, J = 14, 1H, -NH-CH=C).

Anal. Calcd. for C₂₁H₁₉FN₂O₄S: C, 60.86; H, 4.62; N, 6.76. Found: C, 60.62; H, 4.57; N, 6.57.

Ethyl 7-Benzoxazol-2-yl-6-fluoro-4-hydroxyquinoline-3-carboxylate (**10a**).

A mixture of diphenyl ether (100 ml) and compound **9a** (11.1 g, 28.0 mmoles) was heated to reflux and maintained at reflux for 30 minutes. After cooling, the mixture was diluted with an equal volume of *n*-hexane. The precipitate was collected, washed with *n*-hexane and dried (9.50 g, 98%). The product **10a** was recrystallized from *N,N*-dimethylformamide, mp 346-348°; ir (potassium bromide): 3103, 1693, 1618, 1605, 1546, 1527, 1485, 1451, 1381, 1296, 1188, 1034, 807, 744, cm⁻¹; ¹H nmr (deuteriotrifluoroacetic acid): δ 1.57 (t, J = 7 Hz, 3H, CH₃CH₂), 4.75 (q, J = 7 Hz, 2H, CH₂CH₃), 7.90 (m, 2H, aromatic H), 8.06 (m, 2H, aromatic H), 8.65 (d, J = 10 Hz, 1 H, C5H), 9.45 (d, J = 6 Hz, 1 H, C8H), 9.60 (s, 1 H, C2H).

Anal. Calcd. for C₁₉H₁₃FN₂O₄: C, 64.77; H, 3.72; N, 7.95. Found: C, 64.62; H, 3.70; N, 8.02.

Ethyl 7-Benzothiazol-2-yl-6-fluoro-4-hydroxyquinoline-3-carboxylate (**10b**).

A mixture of diphenyl ether (100 ml) and compound **9b** (10.4 g, 25.0 mmoles) was heated to reflux and maintained at reflux for 30 minutes. After cooling, the mixture was diluted with an equal volume of *n*-hexane. The precipitate was collected, washed with *n*-hexane and dried (8.66 g, 94%). The product **10b** was recrystallized from *N,N*-dimethylformamide, mp 333-334°; ir (potassium bromide): 3115, 1693, 1614, 1596, 1548, 1540, 1498, 1297, 1178, 798, 752, 728, 696, cm⁻¹; ¹H nmr

(deuteriotrifluoroacetic acid): δ 1.59 (t, $J = 7$ Hz, 3H, CH_3CH_2), 4.76 (q, $J = 7$ Hz, 2H, CH_2CH_3), 8.05 (m, 2H, aromatic H), 8.39 (m, 2H, aromatic H), 8.69 (d, $J = 11$ Hz, 1 H, C5H), 9.31 (d, $J = 5$ Hz, 1 H, C8H), 9.59 (s, 1 H, C2H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{FN}_2\text{O}_3\text{S}$: C, 61.95; H, 3.56; N, 7.60. Found: C, 61.90; H, 3.50; N, 7.62.

Ethyl 7-Benzoxazol-2-yl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**11a**).

A mixture of compound **10a** (7.04 g, 20.0 mmoles), ethyl iodide (8.1 ml, 100 mmoles), and potassium carbonate (6.90 g, 50.0 mmoles) was suspended in *N,N*-dimethylformamide (100 ml) and heated at 90° for 18 hours. The *N,N*-dimethylformamide was evaporated on the rotary evaporator under reduced pressure. The residue was partitioned between chloroform and water. The chloroform extract was washed with water and saturated sodium chloride. The solution was dried over sodium sulfate and filtered. The solvent was removed at the rotary evaporator. The product was recrystallized from ethyl acetate to yield compound **11a** (6.40 g, 84%), mp $261\text{--}262^\circ$; ir (potassium bromide): 1680, 1651, 1624, 1608, 1604, 1553, 1482, 1446, 1219, 1179, 1096, 1029, 804, 767, 751 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.42 (t, $J = 7$ Hz, 3H, CH_3CH_2), 1.65 (t, $J = 7$ Hz, 3H, CH_3CH_2), 4.44 (m, 4H, 2(CH_2CH_3)), 7.43 (m, 2H, aromatic H), 7.65 (m, 1 H, aromatic H), 7.85 (m, 1 H, aromatic H), 8.35 (d, $J = 11$ Hz, 1 H, C5H), 8.36 (d, $J = 4$, 1 H, C8H), 8.55 (s, 1 H, C2H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_4$: C, 66.31; H, 4.51; N, 7.37. Found: C, 66.29; H, 4.34; N, 7.51.

Ethyl 7-Benzothiazol-2-yl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**11b**).

A mixture of compound **10b** (7.96 g, 20.0 mmoles), ethyl iodide (8.1 ml, 100 mmoles), and potassium carbonate (6.90 g, 50.0 mmoles) was suspended in *N,N*-dimethylformamide (100 ml) and heated at 90° for 18 hours. The *N,N*-dimethylformamide was evaporated on the rotary evaporator under reduced pressure. The residue was partitioned between chloroform and water. The chloroform extract was washed with water and saturated sodium chloride. The solution was dried over sodium sulfate and filtered. The solvent was removed on the rotary evaporator. The product was recrystallized from ethyl acetate/chloroform to yield compound **11b** (3.90 g, 49%), mp $218\text{--}221^\circ$; ir (potassium bromide): 1685, 1638, 1617, 1552, 1484, 1460, 1314, 1220, 1177, 802, 759, 728, cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (t, $J = 7$ Hz, 3H, CH_3CH_2), 1.65 (t, $J = 7$ Hz, 3H, CH_3CH_2), 4.41 (q, $J = 7$ Hz, 4H, 2(CH_2CH_3)), 7.46 (m, 2H, aromatic H), 7.97 (d, $J = 8$ Hz, 1 H, aromatic H), 8.15 (d, $J = 8$ Hz, 1 H, aromatic H), 8.33 (d, $J = 11$ Hz, 1 H, C5H), 8.54 (s, 1 H, C2H), 8.63 (d, $J = 6$ Hz, 1 H, C8H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_3\text{S}$: C, 63.62; H, 4.32; N, 7.07. Found: C, 63.43; H, 4.44; N, 7.21.

7-Benzoxazol-2-yl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**5a**).

A mixture of **11a** (1.90 g, 5.00 mmoles), and 1 *M* sodium hydroxide (5.2 ml) in tetrahydrofuran (60 ml) was heated to reflux and maintained at reflux for six hours. The tetrahydrofuran was removed on the rotary evaporator. Water was added to the residue and the mixture was filtered. The filtrate was acidified with 6*M* hydrochloric acid and the precipitate was collected, washed and dried. The compound was recrystallized from *N,N*-dimethylformamide to yield **5a** (0.65 g, 37%), mp $326\text{--}327^\circ$; ir (potassium bromide): 3671-2365, 1712, 1607, 1558, 1472, 1380,

810, 748 cm^{-1} ; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.84 (t, $J = 7$, 3H, CH_3CH_2), 5.08 (q, $J = 7$, 2H, CH_2CH_3), 7.76-9.25 (m, 6H, aromatic), 9.56 (s, 1H, C2H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{FN}_2\text{O}_4$: C, 64.77; H, 3.72; N, 7.95. Found: C, 64.80; H, 3.87; N, 8.04.

7-Benzothiazol-2-yl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**5b**).

A mixture of **11b** (1.98 g, 5.00 mmoles), and 1 *M* sodium hydroxide (5.2 ml) in tetrahydrofuran (60 ml) was heated to reflux and maintained at reflux overnight. The tetrahydrofuran was removed at the rotary evaporator. Water was added to the residue and the mixture was filtered. The filtrate was acidified with 6*M* hydrochloric acid and the precipitate was collected, washed and dried. The compound was recrystallized from *N,N*-dimethylformamide to yield **5b** (1.31 g, 68%), mp $328\text{--}331^\circ$; ir (potassium bromide): 3681-2020, 1712, 1606, 1542, 1455, 1381, 1180, 809, 768, 737 cm^{-1} ; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.78 (t, $J = 7$, 3H, CH_3CH_2), 5.03 (q, $J = 7$, 2H, CH_2CH_3), 7.94-9.18 (m, 6H, aromatic H), 9.54 (s, 1H, C2H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{FN}_2\text{O}_3\text{S}$: C, 61.95; H, 3.56; N, 7.60. Found: C, 61.71; H, 3.53; N, 7.58.

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